Cerebral Aneurysms and Recurrent TIAs in a 42-Year-Old Patient With DADA2 Mutation

A Case Report

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Abstract

Objectives
Deficiency of adenosine deaminase 2 (DADA2) is a rare, recessively inherited autoinflammatory disease with a wide clinical spectrum of manifestations, including strokes and vasculitis.

Methods
We report a case of a patient with DADA2 who presented with neurologic manifestations.

Results
A 42-year-old woman with a known diagnosis of polyarteritis nodosa experienced several episodes of TIAs. Neuroimaging revealed 2 aneurysms in unusual locations. Her young age, ethnic origin, absent of cardiovascular risk factors, and skin involvement raised the suspicion of DADA2. Genetic testing confirmed the diagnosis, and a directed treatment with anti-TNF was initiated.

Discussion
DADA2, although thought to be rare, needs to be borne in mind when evaluating patients with a combination of neurologic and systemic symptoms, as early diagnosis and treatment are imperative in preventing permanent disability.

Introduction
Deficiency of adenosine deaminase 2 (DADA2) is a rare, recessively inherited autoinflammatory disease of small- and medium-sized blood vessels. The disease was first described in 2014, among Israeli Jewish patients of Georgian ancestry. It is characterized by systemic inflammation, vasculitis, stroke in the young, cytopenias, and immunodeficiency. The ADA2 gene encodes for ADA2, a dimeric extracellular enzyme. It is primarily secreted by cells of myeloid lineage, has catalytic function, presents anti-inflammatory and immunomodulatory properties, and has a role in maintenance of vascular integrity.

Stroke is reported in approximately one-third of patients with DADA2 and may be the initial presenting feature. The incidence of cerebral vascular events is underdiagnosed because of silent infarcts and mild cases of TIAs. Small-sized intracranial aneurysms were also noted in a few patients with DADA2. As opposed to most cerebral aneurysms that tend to be at vascular branch or bifurcation sites, because of decrease in the tunica media and hemodynamic factors, these aneurysms tend to have a peripheral location in nonbranching sites. Some aneurysms self-thrombose spontaneously, but the treatment strategy of those that do not is not established. Although the mechanism of aneurysm formation in the cerebral vessels is still unclear,
vascular endothelial damage of the peripheral blood vessels has been described. The current mechanism hypothesis is the accumulation of inflammatory cytokines as a result of the lack of adenosine deaminase 2 enzymatic activity. It can be assumed that the same process occurs in the cerebral vessels, thus causing cerebral aneurysms.10

DADA2 has a wide clinical spectrum of manifestations that can vary even among families with the same genotype. Treatment with anti-TNF has shown to be effective in controlling inflammation and preserving vascular integrity, thus reducing the risk of ischemic strokes.4

**Clinical Case**

A 42-year-old female patient of Georgian Jewish ancestry presented to the emergency department (ED) with a 48-hour history of recurrent episodes of monocular loss of vision in her left eye (amaurosis fugax). Her medical history included polyarteritis nodosa/leukocytoclastic vasculitis with recurrent limb ulcers treated with steroids in flares, with the last flare being approximately 3 years before the ED visit. She had no cardiovascular risk factors.

Six months before admission, she had an episode of sensorineural hearing loss, treated with steroids, with a consequential mild chronic hearing impairment. MRI conducted at that time was unremarkable, except for a small nonspecific hyperintense lesion at the left parietal lobe.

She was unaware of any hereditary or neurologic diseases in her family but mentioned that her uncle died at a young age from an unknown blood vessel disease.

At the ED, physical and neurologic examination was unremarkable except for a mild livedo reticularis rash on her back and a few subcutaneous nodules on her lower limbs. Non-contrast CT was normal; CT angiography (CTA) showed aneurysmal dilatation of the right M2 artery of 3 mm diameter and 5–6 mm length. A revision of the CTA by an invasive neuroradiologist revealed a second aneurysm at the distal anterior cerebral artery (Figures 1 and 2). Because of multiple distal nonbranching sites of aneurysms, a suspicion of mycotic aneurysms arose. However, echocardiogram showed no vegetations or patent foramen ovale, and the patient had no correlative stigmata (i.e., no fever, sweating, cachexia, or any other manifestations). Fundoscopy ruled out Roth spots, and blood cultures were negative.

MRI + magnetic resonance angiography showed the same aneurysms with preserved brain parenchyma.

Because of her medical history, a rheumatologic workup was performed including the blood test for anti-nuclear antibody, C3, C4, anticardiolipin, anti-B2 glycoprotein, cytoplasmic antineutrophil cytoplasmic antibodies, perinuclear antineutrophil cytoplasmic antibodies, erythrocyte sedimentation rate, and C-reactive protein. All of which were within the normal range, as well as an infectious disease investigation including *Coxiella*, *Brucella*, *Bartonella*, hepatitis, and HIV serologies, which were all negative.

A 3 mm punch skin biopsy of a lower limb nodule showed the preserved epidermis and dermis. Subcutaneous tissue showed fat necrosis without lymphocytic or neutrophilic infiltrate and with no signs of vasculitis. The combination of cutaneous manifestations, along with an episode of sensory-neural hearing loss and recurrent TIAs, suggested a systemic underlying
condition. Because of her Georgian ancestry, DADA2 was suspected, and genetic workup was performed.

A genetic test for DADA2 revealed a mutation of c.1396G>A: p. GLY47Arg; the patient was a homozygous carrier of the mutation. Treatment with anti-TNF medication was initiated. The patient remained asymptomatic as of 10 months after the time of treatment.

We report a case of a 42-year-old woman who was diagnosed with DADA2 mutation after an episode of recurrent amaurosis fugax. She had no cardiovascular risk factors and no clear family history of this disease. Episodic skin manifestation diagnosed as polyarteritis nodosa since childhood; a prior sensorineural hearing loss and 2 nonbranching cerebral aneurysms are probably manifestations of this mutation. The small punch biopsy probably did not include a muscular artery and thus was of limited value.

Phenotypic variability and multisystem involvement make the diagnosis very challenging, and it is therefore underdiagnosed.

Notably, this condition may be fatal because of recurrent ischemic or hemorrhagic strokes and infections.4 Because treatment with anti-TNF was proved to be effective, it is imperative to bear this condition in mind when investigating patients with stroke in the young and atypical nonbranching cerebral aneurysms.

Long-term follow-up of this patient is planned to better understand the natural history of the disease, especially those neurologic manifestations.

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References
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